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Registration Decision RD2010-13

Prothioconazole

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Registration Decision for Prothioconazole

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, and Regulations, is granting full registration for the sale and use of Prothioconazole Technical Fungicide and Proline 480 SC Foliar Fungicide, containing the technical grade active ingredient prothioconazole, for the control or suppression of Ascomycetes, Basidiomycetes and Deuteromycetes diseases on chickpeas, lentils, canola, rapeseed, Oriental mustard, wheat and barley.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1]: Proposed Registration Decision PRD2010-08, *Prothioconazole*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for prothioconazole and summarizes the Agency's decision and the reasons for it. The PMRA received no comments on PRD2010-08. This decision is consistent with the proposed registration decision stated in PRD2010-08.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2010-08, *Prothioconazole* and Regulatory Note REG2007-03, *Prothioconazole* that contain a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act*"...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticide and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Prothioconazole?

The active ingredient prothioconazole and the associated end-use product Proline 480 SC Foliar Fungicide is a systemic fungicide from the Group 3 Fungicides, specifically within the demethylation inhibitor (DMI) class of sterol biosynthesis inhibitors (SBI) fungicides. Proline 480 SC Foliar Fungicide is a foliar-applied fungicide for use on several cereal and vegetable crops, including barley, wheat (spring, durum and winter), canola, rapeseed, Oriental mustard, chickpeas and lentils.

Health Considerations

Can Approved Uses of Prothioconazole Affect Human Health?

Prothioconazole and its metabolite, prothioconazole-desthio, are unlikely to affect your health when used according to label directions.

Potential exposure to prothioconazole and its prothioconazole-desthio metabolite may occur through the diet (food and water) or when handling and applying the product. Prothioconazole and prothioconazole-desthio have a similar toxicological profile with prothioconazole-desthio effects occurring at lower doses. Therefore, the endpoints used for this risk assessment were that of the metabolite. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when prothioconazole (with prothioconazole-desthio) products are used according to label directions.

Prothioconazole and prothioconazole-desthio were considered to be of low acute toxicity by the oral, dermal and inhalation routes in Wistar rats. These compounds were non-irritating when applied to the skin of rabbits. Prothioconazole was considered slightly irritating to the eyes of rabbits while prothioconazole-desthio was non-irritating. The results of skin sensitization testing were negative for both compounds. No signal words are required on the label.

Prothioconazole and prothioconazole-desthio did not cause cancer in animals and were not genotoxic. Decreased motor and locomotor activity were observed following dosing with these compounds. Numerous reproductive effects were also observed. The first signs of toxicity in animals given daily doses of these compounds over longer periods of time were liver, kidney, thyroid and ovary effects. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

When prothioconazole was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indication that the fetus is not more sensitive to this compound than the adult animal. When prothioconazole-desthio was given to pregnant animals, effects on the developing fetus were observed at doses that were not toxic to the mother, indicating that the fetus is more sensitive to this compound than the adult animal. Because of this observation, extra protective measures were applied during the risk assessment to further reduce the allowable level of human exposure to prothioconazole-desthio.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and all infants <1 year old, the subpopulation which would ingest the most prothioconazole relative to body weight, are expected to be exposed to less than 35% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from exposure to prothioconazole residues is not of concern for any of the population sub-groups.

An acute reference dose was determined for the population subgroup of females 13–49 years of age. An aggregate (food and water) dietary intake estimate for females 13–49 years old used less than 85% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established under the authority of the *Food and Drugs Act* through the evaluation of scientific data under the *Pest Control Products Act* (PCPA). Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The poultry feeding study that was submitted to support the conversion from conditional to full registration was reviewed and the data are adequate to establish MRLs in poultry tissues and eggs, as indicated in the Science Evaluation section of this Consultation Document.

Occupational Risks from Handling Proline 480 SC Foliar Fungicide

Occupational risks are not of concern when Proline 480 SC Foliar Fungicide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Proline 480 SC Foliar Fungicide as well as field workers re-entering freshly treated fields can come in direct contact with Proline 480 SC Foliar Fungicide residues on the skin. Therefore, the label specifies that anyone mixing and loading Proline 480 SC Foliar Fungicide must wear long pants, long-sleeved shirts, boots, chemical resistant gloves and protective eyewear. The label also requires that workers do not enter treated fields for 24 hours after application. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, risk to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Prothioconazole Is Introduced into the Environment?

Environmental risks to non-target organisms are not of concern when Proline 480 SC Foliar Fungicide is used according to label directions, which include precautionary label statements and buffer zones.

Prothioconazole and the transformation products prothioconazole-desthio and prothioconazole-*S*-methyl have been considered together in a total toxic residue approach. Total toxic residues of prothioconazole are not expected to persist in soil, nor are they expected to carryover to the next growing season. These compounds have low potential to leach through the soil profile and enter groundwater. Total toxic residues of prothioconazole are not expected to persist in aquatic environments under aerobic conditions, but they are expected to be persistent under anaerobic conditions. Residues of prothioconazole are not expected to be present in air due to its low volatility.

Proline 480 SC Foliar Fungicide, when used according to label directions, does not present a risk to earthworms, bees, beneficial arthropods and other insects, small mammals, birds, and terrestrial plants. However, Proline 480 SC Foliar Fungicide may pose a risk to some aquatic organisms. Precautionary label statements are thus included on the label and buffer zones up to 10 metres are required to mitigate exposure of sensitive aquatic habitats from spray drift.

Value Considerations

What Is the Value of Proline 480 SC Foliar Fungicide?

Proline 480 SC Foliar Fungicide contains prothioconazole, a new active ingredient which will allow for greater alternation of fungicides in an integrated pest management program for foliar diseases of canola, chickpeas and lentils. This will contribute to reducing resistance development in fungal populations.

Proline 480 SC Foliar Fungicide will provide a new chemical mode of action for use in controlling foliar diseases on canola, chickpea and lentils. In addition, suppressing fusarium head blight with Proline 480 SC Foliar Fungicide will also decrease the deoxynivalenol level in wheat and barley, thereby reducing the level of mycotoxin in the grain. This is a direct benefit in the quality of grain destined for animal and human consumption.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Proline 480 SC Foliar Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Proline 480 SC Foliar Fungicide on the skin, anyone mixing and loading Proline 480 SC Foliar Fungicide must wear long pants, long-sleeved shirts, boots, chemical resistant gloves and protective eyewear. In addition, standard label statements to protect against drift during application were added to the label.

Environment

Precautionary label statements are included on the label to identify runoff concerns.

To protect non-target aquatic organisms, precautionary label statements are required on the label and Proline 480 SC Foliar Fungicide cannot be sprayed within up to 10 metres of sensitive aquatic habitats. The distance allowed depends on the method of application and the depth of the aquatic habitat.

Other Information

1. The relevant test data on which the decision is based (as referenced in this document) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.inforserv@hc-sc.gc.ca).

2. Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticide and Pest Management portion of Health Canada's website (Requesting a Reconsideration of Decision, healthcanada.gc.ca/pmra) or contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.inforserv@hc-sc.gc.ca).

[5]As per subsection 35(1) of the *Pest Control Products Act*.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number: 737718
Reference: 2004, Chemistry requirements for the registration of Prothioconazole Technical, Data Numbering Code: 2.0, 2.11.1, 2.11.2, 2.11.3, 2.11.4, 2.12.1, 2.12.2, 2.13.1, 2.13.2, 2.13.3, 2.13.4, 2.14, 2.15 Confidential Business Information

PMRA Document Number: 1775213
Reference: 2005, Material accountability of prothioconazole manufactured in Kansas City, MO, USA, Analytical profile of production batches, Data Numbering Code: 2.13.3 Confidential Business Information

PMRA Document Number: 1787997
Reference: 2005, Material accountability of prothioconazole manufactured in Dormagen / Germany, Analytical profile of production batches, Data Numbering Code: 2.13.3 Confidential Business Information

PMRA Document Number: 1787998
Reference: 2009, Discussion of impurities of special attention in Prothioconazole Technical active substance, Data Numbering Code: 2.13.4 Confidential Business Information

2.0 Human and Animal Health

PMRA Document Number: 1626303
Reference: 2008, Storage stability of prothioconazole and desthio prothioconazole in canola, wheat, mustard greens, turnip root, and tomato fruit, and processed products, Data Numbering Code: 7.3

PMRA Document Number: 1626304
Reference: 2006, Storage stability of JAU6476 and JAU6476-4-hydroxy in bovine fat, Data Numbering Code: 7.5

PMRA Document Number: 1626305
Reference: 2008, Prothioconazole - Magnitude of the residue in laying hens, Data Numbering Code: 7.5

PMRA Document Number: 1626352
Reference: 2007, A developmental neurotoxicity screening study with technical grade SXX 0665 in Wistar rats, Data Numbering Code: 4.5.14